


# Peak oxygen uptake in combination with ventilatory efficiency improve risk stratification in major abdominal surgery

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## Abstract

This pilot study aimed to evaluate if peak  $\text{VO}_2$  and ventilatory efficiency in combination would improve preoperative risk stratification beyond only relying on peak  $\text{VO}_2$ . This was a single-center retrospective cohort study including all patients who underwent cardiopulmonary exercise testing (CPET) as part of preoperative risk evaluation before major upper abdominal surgery during years 2008–2021. The primary outcome was any major cardiopulmonary complication during hospitalization. Forty-nine patients had a preoperative CPET before decision to pursue to surgery (cancer in esophagus [ $n=18$ ], stomach [6], pancreas [16], or liver [9]). Twenty-five were selected for operation. Patients who suffered any major cardiopulmonary complication had lower ventilatory efficiency (i.e., higher  $\text{VE}/\text{VCO}_2$  slope, 37.3 vs. 29.7,  $p=0.031$ ) compared to those without complications. In patients with a low aerobic capacity (i.e., peak  $\text{VO}_2 < 20 \text{ mL/kg/min}$ ) and a  $\text{VE}/\text{VCO}_2$  slope  $\geq 39$ , 80% developed a major cardiopulmonary complication. In this pilot study of patients with preoperative CPET before major upper abdominal surgery, patients who experienced a major cardiopulmonary complication had significantly lower ventilatory efficiency compared to those who did not. A low aerobic capacity in combination with low ventilatory efficiency was associated with a very high risk (80%) of having a major cardiopulmonary complication.

## KEYWORDS

abdominal surgery, cardiopulmonary exercise testing, exercise capacity, functional capacity, ventilatory efficiency

## 1 | INTRODUCTION

A strong association exists between cardiorespiratory fitness and surgical outcomes, where fitter patients possess

heightened resilience to withstand the stress response imposed by major surgery (Roxburgh et al., 2023). Perioperative cardiovascular guidelines endorse preoperative estimation of functional capacity (Halvorsen et al., 2022), but subjective

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assessment by the preoperative physician has a low sensitivity in identifying patients with low functional capacity and is an insufficient predictor of postoperative morbidity and mortality (Wijeyesundera et al., 2018).

Cardiopulmonary exercise testing (CPET) is the gold standard for objective assessment of exercise tolerance and overall cardiopulmonary function (Levett et al., 2018). Studies support the use of CPET for preoperative risk prediction in esophageal/gastric surgery (Benington et al., 2019; Jack et al., 2014), hepatobiliary surgery (Snowden et al., 2010), and pancreatic surgery (Ausania et al., 2012).

Historically, in abdominal surgery, most studies have used either maximal aerobic capacity (peak  $\text{VO}_2$ ) with a threshold of 14 mL/kg/min and/or oxygen uptake ( $\text{VO}_2$ ) at the anaerobic threshold (AT) with a threshold of 11 mL/kg/min to identify patients with a low functional capacity (Wijeyesundera et al., 2018). However, advances in CPET methodology and subsequent research have allowed for identification of other measures of relevance for preoperative risk assessment. In particular, measurement of ventilatory parameters such as the slope of the increase in minute ventilation in relation to carbon dioxide elimination,  $\text{VE}/\text{VCO}_2$  slope (Sun et al., 2002). During the last decade, studies have shown that  $\text{VE}/\text{VCO}_2$  slope may be a stronger marker for postoperative complications and mortality after lung resection compared to peak  $\text{VO}_2$  (Brunelli et al., 2012). CPET has a pivotal role in preoperative guidelines before lung cancer surgery (Brunelli et al., 2013) and incorporation of both peak  $\text{VO}_2$  and ventilatory efficiency in an algorithm to improve risk stratification in lung cancer resection has been proposed (Salati & Brunelli, 2016) and recently validated (Kristenson et al., 2022). This approach has also been suggested for preoperative risk stratification for patients evaluated for abdominal surgery (Sivakumar et al., 2022) but this has to our knowledge not been evaluated.

Therefore, the purpose of this pilot study was to evaluate if stratification of patients' functional capacity using a combination of peak  $\text{VO}_2$  and ventilatory efficiency could improve preoperative risk assessment in major upper abdominal surgery.

## 2 | MATERIAL AND METHODS

### 2.1 | Participants

The study was designed as a single-center retrospective pilot study including all patients who underwent CPET as part of preoperative risk evaluation before major upper abdominal surgery (esophagus, stomach, pancreas, and liver) at Linköping University Hospital in Sweden in 2008–2021 (Table 2). Ethical permission was granted

(DNr 2021-05603-01) and written informed consent was waived by the ethics committee.

### 2.2 | Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was performed on a bicycle ergometer (eBike Basic, GE Medical Systems, GmbH), aiming at maximal exhaustion after 8–12 min. The workload was chosen individually (based on standard clinical practice, which accounts for self-reported fitness alongside clinical judgment) with a 5-min warm-up phase between 10 and 50 watts and an incremental ramp protocol with a workload increase of 10–20 watts/min. During CPET, patients were monitored with ECG (Marquette CASE 8000, GE Medical Systems) and repeated systolic blood pressure measurements. The Borg rating of perceived exertion (RPE) scale (Ausania et al., 2012; Benington et al., 2019; Brunelli et al., 2012; Brunelli et al., 2013; Dindo et al., 2004; Fernandez et al., 2015; Gläser et al., 2013; Gläser et al., 2010; Kristenson et al., 2022; Medinger et al., 2001; Salati & Brunelli, 2016; Sivakumar et al., 2022; Snowden et al., 2010; Sun et al., 2002; Wasserman et al., 1996) was used to quantify perceived exhaustion, and the Borg CR-10 scale was used to assess chest pain and dyspnoea. Blood pressure as well as RPE, dyspnea, and chest-pain ratings were performed every 2–3 min during the test.

Gas exchange and ventilatory variables were measured breath by breath (Jaeger Oxycon Pro or Vyntus CPX; Viasys Healthcare). The system was calibrated before each CPET. Oxygen uptake ( $\text{VO}_2$ ), carbon dioxide elimination ( $\text{VCO}_2$ ), and ventilation (VE) were presented as 10-s means, excluding the breaths with the highest and lowest values. Peak  $\text{VO}_2$  was defined as the average of the two highest consecutive 10-s mean  $\text{VO}_2$  intervals at or close to the end of the exercise and was presented as absolute values (mL/min) as well as relative values (mL/kg/min and percent of predicted [% predicted]) (Gläser et al., 2010). Maximum achieved workload was presented as peak power (measured in Watt) as well as % predicted peak power (Gläser et al., 2013).

To obtain ventilatory variables ( $\text{VE}/\text{VCO}_2$  slope and the nadir of the ventilatory equivalent of carbon dioxide [ $\text{EqCO}_2$ ]), automated slopes using a commercial software (Sentry Suite 3.10; CareFusion GmbH) were used, and these were manually adjusted if deemed necessary by the reviewer.  $\text{VE}/\text{VCO}_2$  slope was defined as the slope of the increase in VE relative to  $\text{VCO}_2$  increase during the linear portion of the curve up until the respiratory compensation point.  $\text{EqCO}_2$  nadir was defined as the lowest (i.e., nadir) value of  $\text{VE}/\text{VCO}_2$  during exercise. The  $\text{VO}_2$  at the anaerobic threshold (AT) was determined manually. We used a combination of the V-slope method (1st deflection) and

evaluation of the ventilatory equivalents of  $\text{VO}_2$  and  $\text{VCO}_2$ , where the AT was defined as where  $\text{VE}/\text{VO}_2$  started to increase before an increase in  $\text{VE}/\text{VCO}_2$  (Levett et al., 2018).

First, patients were grouped based on previously suggested thresholds into either a low or high-risk group, according to peak  $\text{VO}_2$  (low risk:  $\geq 14$ , high risk:  $< 14$ ),  $\text{VO}_2$  at AT (low risk:  $\geq 11$ , high risk:  $< 11$ ), and  $\text{VE}/\text{VCO}_2$  slope (low risk:  $< 39$ , high risk:  $\geq 39$ ). Second, patients were grouped into three risk groups applying a joint assessment of peak  $\text{VO}_2$  and  $\text{VE}/\text{VCO}_2$  slope as Group 1 (low risk): peak  $\text{VO}_2 \geq 20$  mL/kg/min, Group 2 (intermediate risk): peak  $\text{VO}_2 < 20$  mL/kg/min and  $\text{VE}/\text{VCO}_2$  slope  $< 39$ , and Group 3 (high risk): peak  $\text{VO}_2 < 20$  mL/kg/min and  $\text{VE}/\text{VCO}_2$  slope  $\geq 39$ . Patients' comorbidities (coronary artery disease, current treatment for heart failure, current treatment for arrhythmia, valvular disease, current treatment for hypertension, previous cerebrovascular insult, chronic obstructive pulmonary disease, chronic kidney failure, or diabetes mellitus) were determined by retrospective journal evaluation and followed international recommendations for use of terminology (Fernandez et al., 2015).

## 2.3 | Outcome definitions

The primary outcome was any major cardiopulmonary complication following surgery from admittance to discharge, further defined in Table 1.

Secondary outcomes were Clavien-Dindo complications  $>$  grade 2 (complications requiring surgical, endoscopic or radiological intervention with or without general anesthesia, life-threatening complications that require intensive care or death of the patient; Dindo et al., 2004), length of hospital stay, and 90 day mortality.

## 2.4 | Statistical analysis

Statistical analysis was performed using SPSS 27.0.0.0 (IBM-SPSS Inc.). Due to the low number of observations, non-parametrical statistics were used. Median values were presented with corresponding interquartile range (IQR) and compared with the independent-samples Mann-Whitney  $U$  test and frequencies were compared with Fischer's exact test. All tests were two-sided, and the significance level was set at  $p < 0.05$ .

## 3 | RESULTS

In total, 49 patients were included, as they had performed a preoperative CPET before the decision regarding if the patient would pursue to major upper abdominal surgery

**TABLE 1** Definition of study primary outcome.

The primary outcome was any major cardiopulmonary complication following surgery until discharge and included either of

(a) A major adverse cardiovascular event<sup>a</sup>

- cardiac death
- cerebrovascular death
- non-fatal cardiac arrest
- acute myocardial infarction
- congestive heart failure
- new cardiac arrhythmia
- angina, or stroke

(b) A major postoperative pulmonary complication<sup>b</sup>

- Pneumonia (patient has received antibiotics for a suspected respiratory infection and met one or more of the following criteria: new or changed sputum, new or changed lung opacities, fever, white blood cell count  $< 4 \times 10^9/\text{L}$  or  $> 12 \times 10^9/\text{L}$ )
- Moderate respiratory failure (hypoxia requiring continuous positive airway pressure, non-invasive ventilation, high-flow nasal cannula or intubation)
- Acute respiratory distress syndrome defined by the Berlin criteria<sup>c</sup>
- Atelectasis recurring bronchoscopy

(c) Pulmonary embolism (verified with computed tomography pulmonary angiography)

<sup>a</sup>Defined as suggested by Sabaté et al. (2011).

<sup>b</sup>Modified by the definition of Briez et al. (2012).

<sup>c</sup>Defined as suggested by ARDS Definition Task Force et al. (2012).

or not (Figure 1). The median age was 73 years (range 43–88 years, IQR 68–79), and 74% were men ( $n = 36$ ). Patients were included due to cancer in the esophagus ( $n = 18$ ), stomach ( $n = 6$ ), pancreas ( $n = 16$ ), or liver ( $n = 9$ ).

## 3.1 | CPET in patient selected for operation versus not selected for operation

Twenty-five of the 49 patients were selected for operation due to cancer in esophagus ( $n = 10$ ), stomach ( $n = 4$ ), pancreas ( $n = 10$ ), and liver ( $n = 1$ ). In patients selected for operation, the median age was 73 years (IQR 67–80), and 68% were men ( $n = 17$ ). The median values and IQR for peak  $\text{VO}_2$ , AT, and  $\text{VE}/\text{VCO}_2$  slope were 18.5 (16.0–22.7) mL/kg/min, 12.8 (11.2–15.6) mL/kg/min, and 30.8 (29.0–37.4).

No statistically significant differences were found in median age (73.0 vs. 73.5,  $p = 0.67$ ) or in presence of comorbidities between patients selected for operation compared to the non-operated group (Figure 1 and Appendix 1). However, in general, patients not selected for operation

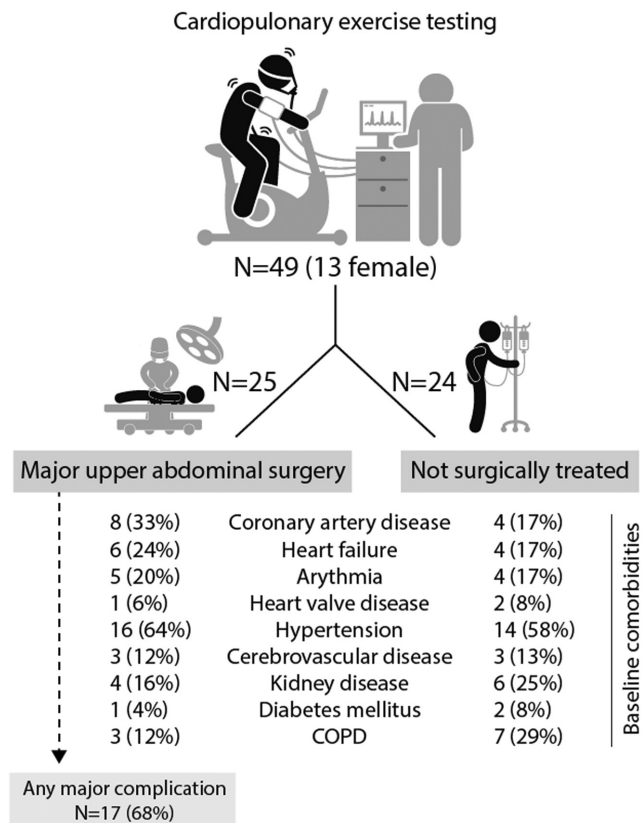


FIGURE 1 Flowchart of study.

had less favorable CPET data including significantly lower values of peak power and peak  $\text{VO}_2$  and higher  $\text{VE}/\text{VCO}_2$  slope (Appendix 2).

### 3.2 | CPET in patients with versus without complications

In total, the frequency of major cardiopulmonary complications or a complication, according to Clavien–Dindo, was 32% ( $N=8$ ) and 48% ( $N=12$ ), respectively. No patient died within 90 days after surgery. The median length of stay was 11 days (IQR 8–22).

No differences were found in presence of comorbidities between patients who suffered a major cardiopulmonary complication compared to those who did not (Table 2). Also, when comparing the median values of preoperative CPET measures, no differences were found in peak power, peak  $\text{VO}_2$ , or  $\text{VO}_2$  at AT for patients who suffered a major cardiopulmonary complication compared to those who did not. In contrast, higher (less favorable) values of  $\text{VE}/\text{VCO}_2$  slope and  $\text{EqCO}_2$  nadir were present in patients who suffered a major cardiopulmonary complication (Table 3). When analyzing patients who did or did not suffer a complication > grade 2 according to the Clavien–Dindo classification, lower (less

favorable) values were found for % predicted peak power and % predicted peak  $\text{VO}_2$  in patients who experienced a complication (Table 4).

#### 3.2.1 | Risk stratification

There were statistically non-significant trends that patients with low peak  $\text{VO}_2$  or  $\text{VO}_2$  at AT or high  $\text{VE}/\text{VCO}_2$  slope values (defined by previously suggested thresholds) had an increased frequency of complications (Figure 2). However, when using a combined stratification by peak  $\text{VO}_2$  and  $\text{VE}/\text{VCO}_2$  slope, patients with peak  $\text{VO}_2 < 20 \text{ mL/kg/min}$  and  $\text{VE}/\text{VCO}_2$  slope  $\geq 39$  (group 3, higher risk) had a statistically significant higher rate of major cardiopulmonary complications and longer length of stay compared to the other risk groups (Figure 3).

## 4 | DISCUSSION

In this pilot study of patients who performed CPET before major upper abdominal surgery, we found that patients who suffered a major cardiopulmonary complication had significantly higher (less favorable) values of ventilatory efficiency compared to those who did not sustain a complication. Importantly, we found that by using a combination of low aerobic capacity (peak  $\text{VO}_2 < 20 \text{ mL/kg/min}$ ) and ventilatory efficiency ( $\text{VE}/\text{VCO}_2\text{-slope} \geq 39$ ), we were able to identify a group of patients with a particularly high frequency of complications (80%).

Of note, we did not find any significant differences in age or in prevalence of comorbidities in patients selected versus those not selected for surgery. However, patients not selected for surgery were found to have a lower functional capacity, reflected by less favorable results on multiple CPET measures (lower aerobic capacity, ventilatory efficiency as well as anaerobic threshold). When analyzing the risk of postoperative cardiopulmonary complications, again, no differences were found in prevalence of comorbidities between patients who suffered a complication compared to those who did not. However, when comparing the median values of preoperative CPET measures, higher (less favorable) values of  $\text{VE}/\text{VCO}_2$  slope and  $\text{EqCO}_2$  nadir were present in patients who suffered a major cardiopulmonary complication. Interestingly, no differences were found in the more traditional measures peak power, peak  $\text{VO}_2$ , or  $\text{VO}_2$  at AT for patients who suffered a major cardiopulmonary complication compared to those who did not. These results harmonize with the results from a large multicenter study where the thresholds peak  $\text{VO}_2$   $14 \text{ mL/kg/min}$  and  $\text{VO}_2$  at AT  $11 \text{ mL/kg/}$

**TABLE 2** Distribution of gender, comorbidities, and anthropometrics for patients with or without postoperative major cardiopulmonary complications.

	No cardiopulmonary complication		Cardiopulmonary complication		
	<i>N</i>	%	<i>N</i>	%	<i>p</i>
Gender					
Women	6	35	2	25	0.61
Men	11	65	6	75	
Comorbidity					
Coronary artery disease	6	35	2	25	0.61
Heart failure	4	24	2	25	0.94
Arrythmia	4	24	1	13	0.52
Valvular disease	1	6	0	0	0.48
Hypertension	9	53	7	88	0.09
Cerebrovascular insult	1	6	2	25	0.17
COPD	3	18	1	13	0.74
Kidney failure	1	6	0	0	0.48
Diabetes mellitus	1	6	2	25	0.17
Anthropometrics		Median (IQR)	Median (IQR)		<i>p</i>
Height, cm	17	172 (165–177)	8	175 (169–183)	0.45
Weight, kg	17	73 (64–85)	8	82 (74–100)	0.09
Body mass index, kg/m <sup>2</sup>	17	24.9 (23.4–27.3)	8	25.7 (24.3–34.3)	0.17

Abbreviations: COPD, Chronic obstructive pulmonary disease; IQR, interquartile range; *p*, Fischer's exact test.

**TABLE 3** Results from preoperative cardiopulmonary exercise testing for patients with or without postoperative major cardiopulmonary complications.

	Total			No cardiopulmonary complication			Cardiopulmonary complication			<i>p</i>
	<i>N</i>	Median	IQR	<i>N</i>	Median	IQR	<i>N</i>	Median	IQR	
Peak power, watt	25	100.0	81.0–132.0	17	100.0	81.0–128.0	8	98.0	68.8–145.3	0.88
% predicted peak Power, %	25	68	55–92	17	68	58–90	8	68	51–92	0.68
Peak VO <sub>2</sub> , mL/min	25	1356	1140–1833	17	1315	1140–1833	8	1599	1121–1855	0.56
Peak VO <sub>2</sub> , mL/kg/min	25	18.5	15.3–22.4	17	18.5	16.0–23.3	8	18.7	12.9–20.7	0.56
% predicted peak VO <sub>2</sub> , %	25	91	70–104	17	92	71–105	8	84	70–99	0.60
VO <sub>2</sub> at AT, mL/kg/min	24	12.8	11.2–15.6	17	13.2	11.5–15.8	7	12.1	9.1–15.2	0.30
VE/VCO <sub>2</sub> slope	25	30.8	29.0–37.4	17	29.7	28.6–34.9	8	37.3	31.1–45.1	0.03
EqCO <sub>2</sub> nadir	25	30.8	27.9–34.7	17	29.1	27.6–33.6	8	35.0	31.1–40.1	0.048

Abbreviations: EqCO<sub>2</sub>, ventilatory equivalent for carbon dioxide; IQR, interquartile range; *p*, Independent-Samples Mann–Whitney *U* Test; VCO<sub>2</sub>, carbon dioxide elimination; VE, minute ventilation; VO<sub>2</sub>peak, peak oxygen uptake.

min were not significantly related to an increased risk for the primary outcome (death or myocardial infarction within 30 days after surgery; Wijeyesundera et al., 2018). This stresses the importance in using relevant measures and thresholds in preoperative CPET studies.

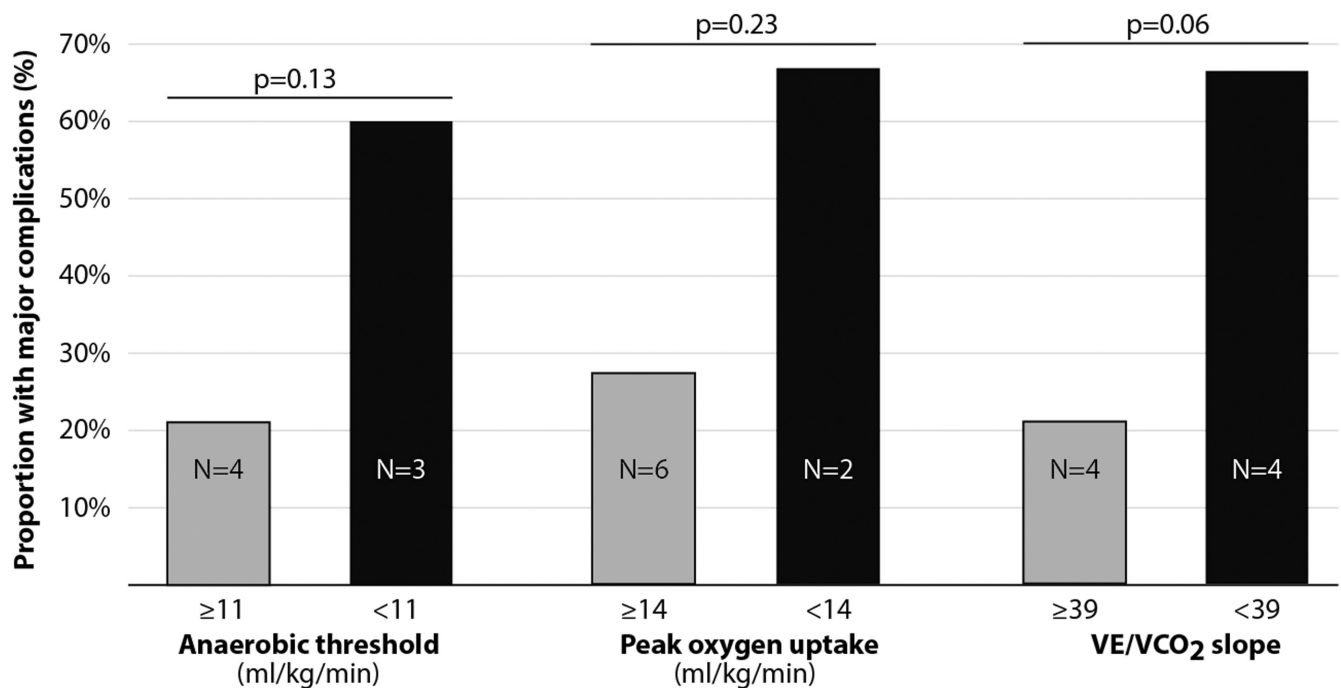
Interestingly, the strongest risk prediction was found when combining the two measures peak VO<sub>2</sub> and VE/VCO<sub>2</sub>-slope. This has been evaluated with promising results in thoracic surgery (Kristenson et al., 2022), but this is, to our knowledge, the first study adopting this



**TABLE 4** Results from preoperative cardiopulmonary exercise test for patients with or without any postoperative complication according to Clavien–Dindo > grade 2.

	Postoperative complication			No postoperative complication			<i>p</i>
	<i>N</i>	Median	IQR	<i>N</i>	Median	IQR	
Peak power, Watt	12	90.5	80.8–114	13	113	71.5–142	0.40
% predicted peak power, %	12	62	54–75	13	85	60.5–100	0.04
Peak VO <sub>2</sub> , mL/min	12	1354	1122–1655	13	1682	1092–1961	0.44
Peak VO <sub>2</sub> , mL/kg/min	12	16.6	14.9–19.7	13	21.8	16.0–25.8	0.01
% predicted peak VO <sub>2</sub> , %	12	82	66–92	13	104	81.108	0.03
VO <sub>2</sub> at AT, mL/kg/min	11	12.1	11.4–14.2	13	14.4	10.7–17.0	0.25
VE/VCO <sub>2</sub> slope	12	32.8	29.4–41.7	13	30.5	27.5–34.9	0.26
EqCO <sub>2</sub> nadir	12	32.7	29.5–37.9	13	28.7	25.7–33.4	0.05

Abbreviations: EqCO<sub>2</sub>, ventilatory equivalent for carbon dioxide; IQR, interquartile range; *p*, Independent-Samples Mann–Whitney *U* Test for comparison between patients who sustained versus did not sustain a postoperative complication; VO<sub>2</sub>peak, peak oxygen uptake; VCO<sub>2</sub>, carbon dioxide elimination; VE, minute ventilation.



**FIGURE 2** Proportion of patients who suffered or did not suffer a major cardiopulmonary complication after surgery stratified by traditional thresholds for measures from the preoperative cardiopulmonary exercise test. Frequencies of complications were compared with Fischer's exact test.

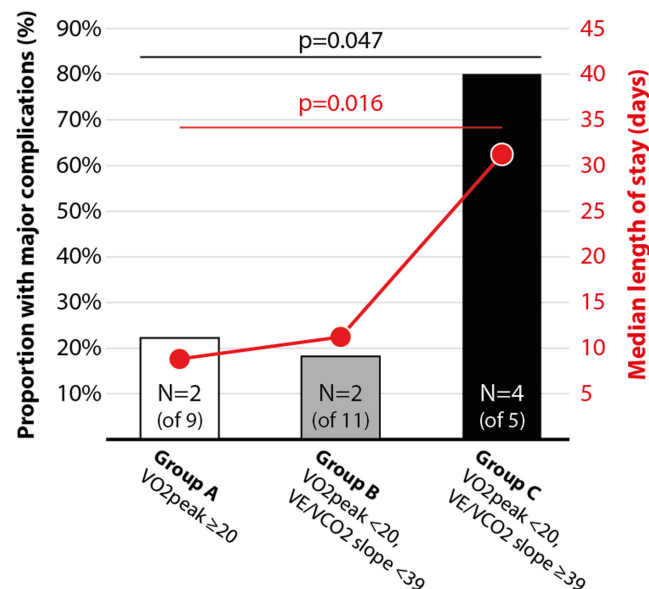
approach in risk stratifications studies within major abdominal surgery.

#### 4.1 | Ventilatory efficiency

Ideally, in the lung, there is a perfect match between perfusion and ventilation. When a mismatch occurs, gas exchange is impaired, and a greater ventilation is requiring for a given output of CO<sub>2</sub>. This ventilatory inefficiency

(most often due to increased dead space ventilation) is reflected as an increase in VE/VCO<sub>2</sub> slope measured during CPET (Sun et al., 2002). For example, a VE/VCO<sub>2</sub> slope value of 39 means that a patient needs to exhale 39 liters of air to eliminate 1 liter of CO<sub>2</sub>. VE/VCO<sub>2</sub> slope has in recent decades emerged as a tool to assess both the presence and severity of heart or lung disease (Medinger et al., 2001; Wasserman et al., 1996).

VE/VCO<sub>2</sub> slope determination was first used by cardiologists evaluating patients with heart failure (Sun



**FIGURE 3** Proportion of patients who suffered or did not suffer a major cardiopulmonary complication after surgery and length of hospital stay for patients from different risk groups based on VO<sub>2</sub>peak (peak oxygen consumption) measured in mL/kg/min, and VE/VCO<sub>2</sub>-slope (ventilatory efficiency) from the preoperative cardiopulmonary exercise test. Median values of length of stay were compared with the Independent-Samples Mann–Whitney *U* Test and frequencies of complications were compared with Fischer’s Exact Test.

et al., 2002). Therefore, most studies using CPET for preoperative risk stratification refer to thresholds of VE/VCO<sub>2</sub> slope generated from historical data in heart failure patients (Chua et al., 1997; Corrà et al., 2002), most often using a cutoff of 35 to identify high-risk patients (Brunelli et al., 2012; Shafiek et al., 2016). Recent studies in major abdominal surgery have identified patients with a VE/VCO<sub>2</sub> slope ≥ 39 to have an increased risk of mortality (Wilson et al., 2019) and this threshold was therefore used in the current study. However, as previous authors have suggested, using a single threshold entails a binary approach toward risk assessment, which is problematic in the real, more complex practice of preoperative CPET (Older, 2013; Sivakumar et al., 2022). Therefore, future studies in larger cohorts should strive to identify multiple thresholds that privilege sensitivity and specificity separately (Wilson, 2018).

## 4.2 | Clinical implication

Cardiopulmonary exercise testing has several advantages compared to other means of assessing functional capacity. First, it is possible to determine whether the test was at maximal effort by the patient, which is essential if maximum functional capacity is to be evaluated

(such as peak VO<sub>2</sub>). Second, during CPET, several other variables of importance than maximum capacity can be assessed, such as signs of coronary artery disease, pulmonary comorbidities or ventilatory inefficiency. Third, several of these variables, including VE/VCO<sub>2</sub> slope is measured at submaximal effort and thus does not require a truly maximal test. Future studies should focus on which patients that can be assessed by screening with a more widely available functional test, and which patients benefit from the more comprehensive CPET (Junttila et al., 2022).

After having identified patients at particularly high risk for major cardiopulmonary complications, how can the perioperative physician translate these results to clinical decision-making, ultimately decreasing the risk for the individual patient? First, prehabilitation can be initiated which has been shown to increase functional capacity and lower the risk of complications and mortality for patients undergoing abdominal surgery (Pang et al., 2022; Zarate Rodriguez et al., 2023). Of note, exercise training has been shown to increase not only VO<sub>2</sub> peak, but also ventilatory efficiency (i.e., lowering VE/VCO<sub>2</sub> slope) for patients with heart failure or pulmonary hypertension (Mehani & Abdeen, 2017). It remains to be evaluated whether preoperative risk defined by the combination of peak VO<sub>2</sub> and VE/VCO<sub>2</sub> slope can be affected by prehabilitation in abdominal surgery. Second, if a previously unknown pathology is identified, treatment can be initiated to treat the underlying condition. Third, the data derived from CPET may be used to inform collaborative decision-making and contribute to preoperative risk assessment (Levett et al., 2018). Fourth, high-risk patients that proceed to operation should be assessed and evaluated with caution to identify complications before severe organ failure occurs, a situation that has been called the “failure of rescue” (Ghaferi et al., 2009). Previous studies in colorectal patients have showed that patients preoperatively identified as having an intermediary risk for postoperative complications, the risk was dependent on whether they were treated on a high dependency unit or a standard postoperative ward (Swart et al., 2017). This could in turn speak in favor of having different postoperative care or readiness for complications depending on preoperative risk assessment, where CPET may play an important role.

## 4.3 | Limitations

This is a retrospective, single center pilot study with the aim of exploring if strategies for risk stratification used in thoracic surgery also could be applied in a major upper abdominal surgery cohort. Thus, the total sample is small, and the results should therefore be interpreted with

caution. The low power did not allow for any adjustment for other preoperative comorbidities, although there were no statistically significant differences in frequencies of comorbidities between patients who sustained a major cardiopulmonary complication compared to those who did not. The small sample size also precluded stratification by the different types of cancers included, which should be considered in future studies including more patients.

## 5 | CONCLUSION

Patients who suffered a major cardiopulmonary complication following major upper abdominal surgery had significantly lower (worse) ventilatory efficiency at preoperative CPET compared to those who did not. Having a low ventilatory efficiency in combination with a low aerobic capacity was associated with a particularly high risk (80%) of suffering a major cardiopulmonary complication. The results from this pilot study calls for validation in larger studies in order to further improve risk assessment in this group of patients.

## AUTHOR CONTRIBUTION

KK is the guarantor of the study. EG performed the data collection for the study. KK and EG performed data analyses. KK and EG drafted the first version of the manuscript. All authors listed have provided substantial contributions to the conception, design, data acquisition, analysis, and interpretation of this work, and all authors participated in revising the manuscript after critical review. All authors approved the final version of the manuscript.

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## CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

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## REFERENCES

- ARDS Definition Task Force, Ranieri, V. M., Rubenfeld, G. D., Thompson, B. T., Ferguson, N. D., Caldwell, E., Fan, E., Camporota, L., & Slutsky, A. S. (2012). Acute respiratory distress syndrome: The Berlin Definition. *JAMA*, 307(23), 2526–2533.
- Ausania, F., Snowden, C. P., Prentis, J. M., Holmes, L. R., Jaques, B. C., White, S. A., French, J. J., Manas, D. M., & Charnley, R. M. (2012). Effects of low cardiopulmonary reserve on pancreatic leak following pancreaticoduodenectomy. *The British Journal of Surgery*, 99(9), 1290–1294.
- Benington, S., Bryan, A., Milne, O., & Alkhaffaf, B. (2019). CPET and cardioesophagectomy: A single Centre 10-year experience. *European Journal of Surgical Oncology*, 45(12), 2451–2456.
- Briez, N., Piessen, G., Torres, F., Lebuffe, G., Triboulet, J. P., & Mariette, C. (2012). Effects of hybrid minimally invasive oesophagectomy on major postoperative pulmonary complications. *Journal of British Surgery*, 99(11), 1547–1553.
- Brunelli, A., Belardinelli, R., Pompili, C., Xiume, F., Refai, M., Salati, M., & Sabbatini, A. (2012). Minute ventilation-to-carbon dioxide output (VE/VCO<sub>2</sub>) slope is the strongest predictor of respiratory complications and death after pulmonary resection. *The Annals of Thoracic Surgery*, 93(6), 1802–1806.
- Brunelli, A., Kim, A. W., Berger, K. I., & Addrizzo-Harris, D. J. (2013). Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*, 143(5 Suppl), e166S–e190S.
- Chua, T. P., Ponikowski, P., Harrington, D., Anker, S. D., Webb-Peploe, K., Clark, A. L., Poole-Wilson, P. A., & Coats, A. J. S. (1997). Clinical correlates and prognostic significance of the ventilatory response to exercise in chronic heart failure. *Journal of the American College of Cardiology*, 29(7), 1585–1590.
- Corrà, U., Mezzani, A., Bosimini, E., Scapellato, F., Imparato, A., & Giannuzzi, P. (2002). Ventilatory response to exercise improves risk stratification in patients with chronic heart failure and intermediate functional capacity. *American Heart Journal*, 143(3), 418–426.
- Dindo, D., Demartines, N., & Clavien, P. A. (2004). Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of Surgery*, 240(2), 205–213.
- Fernandez, F. G., Falcoz, P. E., Kozower, B. D., Salati, M., Wright, C. D., & Brunelli, A. (2015). The Society of Thoracic Surgeons and the European Society of Thoracic Surgeons general thoracic surgery databases: Joint standardization of variable definitions and terminology. *The Annals of Thoracic Surgery*, 99(1), 368–376.
- Ghaferi, A. A., Birkmeyer, J. D., & Dimick, J. B. (2009). Variation in hospital mortality associated with inpatient surgery. *The New England Journal of Medicine*, 361(14), 1368–1375.
- Gläser, S., Ittermann, T., Schäper, C., Obst, A., Dörr, M., Spielhagen, T., Felix, S. B., Völzke, H., Bollmann, T., Opitz, C. F., Warnke, C., Koch, B., & Ewert, R. (2013). The study of health in Pomerania (SHIP) reference values for cardiopulmonary exercise testing. *Pneumologie*, 67(1), 58–63.
- Gläser, S., Koch, B., Ittermann, T., Schäper, C., Dörr, M., Felix, S. B., Völzke, H., Ewert, R., & Hansen, J. E. (2010). Influence of age, sex, body size, smoking, and beta blockade on key gas exchange exercise parameters in an adult population. *European Journal of Cardiovascular Prevention and Rehabilitation*, 17(4), 469–476.
- Halvorsen, S., Mehilli, J., Cassese, S., Hall, T. S., Abdelhamid, M., Barbato, E., de Hert, S., de Laval, I., Geisler, T., Hinterbuchner, L., Ibanez, B., Lenarczyk, R., Mansmann, U. R., McGreavy, P., Mueller, C., Muneretto, C., Niessner, A., Potpara, T. S., Ristić,



- A., ... Touyz, R. M. (2022). 2022 ESC guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. *European Heart Journal*, 43(39), 3826–3924.
- Jack, S., West, M. A., Raw, D., Marwood, S., Ambler, G., Cope, T. M., Shrotri, M., Sturgess, R. P., Calverley, P. M. A., Ottensmeier, C. H., & Grocott, M. P. W. (2014). The effect of neoadjuvant chemotherapy on physical fitness and survival in patients undergoing oesophagogastric cancer surgery. *European Journal of Surgical Oncology*, 40(10), 1313–1320.
- Junttila, A., Helminen, O., Mrena, J., & Sihvo, E. (2022). Exercise capacity in the stair-climbing test predicts outcomes of operable esophageal cancer in minimally invasive era. *European Journal of Surgical Oncology*, 48(3), 589–596.
- Kristenson, K., Hylander, J., Boros, M., Fyrenius, A., & Hedman, K. (2022). Ventilatory efficiency in combination with peak oxygen uptake improves risk stratification in patients undergoing lobectomy. *JTCVS Open*, 11, 317–326.
- Levett, D. Z. H., Jack, S., Swart, M., Carlisle, J., Wilson, J., Snowden, C., Riley, M., Danjoux, G., Ward, S. A., Older, P., Grocott, M. P. W., & Perioperative Exercise Testing and Training Society (POETTS). (2018). Perioperative cardiopulmonary exercise testing (CPET): Consensus clinical guidelines on indications, organization, conduct, and physiological interpretation. *British Journal of Anaesthesia*, 120(3), 484–500.
- Medinger, A. E., Khouri, S., & Rohatgi, P. K. (2001). Sarcoidosis: The value of exercise testing. *Chest*, 120(1), 93–101.
- Mehani, S. H. M., & Abdeen, H. A. A. (2017). Cardiopulmonary rehabilitation program impact on prognostic markers in selected patients with resting and exercise-induced ventilatory inefficiency: A clinical trial. *Journal of Physical Therapy Science*, 29(10), 1803–1810.
- Older, P. (2013). Anaerobic threshold, is it a magic number to determine fitness for surgery? *Perioperative Medicine (Lond)*, 2(1), 2.
- Pang, N. Q., Tan, Y. X., Samuel, M., Tan, K. K., Bonney, G. K., Yi, H., & Kow, W. C. A. (2022). Multimodal prehabilitation in older adults before major abdominal surgery: A systematic review and meta-analysis. *Langenbeck's Archives of Surgery*, 407(6), 2193–2204.
- Sabaté, S., Mases, A., Guiler, N., Canet, J., Castillo, J., Orrego, C., Sabaté, A., Fita, G., Parramón, F., Paniagua, P., Rodríguez, A., & Sabaté, M. (2011). Incidence and predictors of major perioperative adverse cardiac and cerebrovascular events in non-cardiac surgery. *British Journal of Anaesthesia*, 107(6), 879–890.
- Roxburgh, B. H., Cotter, J. D., Campbell, H. A., Reymann, U., Wilson, L. C., Gwynne-Jones, D., van Rij, A. M., & Thomas, K. N. (2023). Physiological relationship between cardiorespiratory fitness and fitness for surgery: A narrative review. *British Journal of Anaesthesia*, 130(2), 122–132.
- Salati, M., & Brunelli, A. (2016). Risk stratification in lung resection. *Current Surgery Reports*, 4(11), 37.
- Shafiek, H., Valera, J. L., Togores, B., Torrecilla, J. A., Saulea, J., & Cosio, B. G. (2016). Risk of postoperative complications in chronic obstructive lung diseases patients considered fit for lung cancer surgery: Beyond oxygen consumption. *European Journal of Cardio-Thoracic Surgery*, 50(4), 772–779.
- Sivakumar, J., Forshaw, M. J., Lam, S., Peters, C. J., Allum, W. H., Whibley, J., Sinclair, R. C. F., Snowden, C. P., Hii, M. W., Sivakumar, H., & Read, M. (2022). Identifying the limitations of cardiopulmonary exercise testing prior to esophagectomy using a pooled analysis of patient-level data. *Diseases of the Esophagus*, 35(11), doac005. <https://doi.org/10.1093/dote/doac005>
- Snowden, C. P., Prentis, J. M., Anderson, H. L., Roberts, D. R., Randles, D., Renton, M., & Manas, D. M. (2010). Submaximal cardiopulmonary exercise testing predicts complications and hospital length of stay in patients undergoing major elective surgery. *Annals of Surgery*, 251(3), 535–541.
- Sun, X. G., Hansen, J. E., Garatachea, N., Storer, T. W., & Wasserman, K. (2002). Ventilatory efficiency during exercise in healthy subjects. *American Journal of Respiratory and Critical Care Medicine*, 166(11), 1443–1448.
- Swart, M., Carlisle, J. B., & Goddard, J. (2017). Using predicted 30 day mortality to plan postoperative colorectal surgery care: A cohort study. *British Journal of Anaesthesia*, 118(1), 100–104.
- Wasserman, K., Zhang, Y. Y., & Riley, M. S. (1996). Ventilation during exercise in chronic heart failure. *Basic Research in Cardiology*, 91(Suppl 1), 1–11.
- Wijesundera, D. N., Pearse, R. M., Shulman, M. A., Abbott, T. E. F., Torres, E., Ambosta, A., Croal, B. L., Granton, J. T., Thorpe, K. E., Grocott, M. P. W., Farrington, C., Myles, P. S., Cuthbertson, B. H., Wallace, S., Thompson, B., Ellis, M., Borg, B., Kerridge, R. K., Douglas, J., ... Wijesundera, H. C. (2018). Assessment of functional capacity before major non-cardiac surgery: An international, prospective cohort study. *Lancet*, 391(10140), 2631–2640.
- Wilson, R. J. T. (2018). Shades of grey: Embracing uncertainty in the exercise room. *British Journal of Anaesthesia*, 120(6), 1145–1146.
- Wilson, R. J. T., Yates, D. R. A., Walkington, J. P., & Davies, S. J. (2019). Ventilatory inefficiency adversely affects outcomes and longer-term survival after planned colorectal cancer surgery. *British Journal of Anaesthesia*, 123(2), 238–245.
- Zarate Rodriguez, J. G., Cos, H., Koenen, M., Cook, J., Lmsw, C. K., Raper, L., Guthrie, T., Strasberg, S. M., Hawkins, W. G., Hammill, C. W., Fields, R. C., Chapman, W. C., Eberlein, T. J., Kozower, B. D., & Sanford, D. E. (2023). Impact of Prehabilitation on postoperative mortality and the need for non-home discharge in high-risk surgical patients. *Journal of the American College of Surgeons*, 237, 558–567.

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## APPENDIX 1

### DISTRIBUTION OF GENDER, COMORBIDITIES AND ANTHROPOMETRICS AMONG PATIENTS WHO WERE AND WERE NOT SELECTED FOR OPERATION.

	Total		Not selected for surgery		Selected for surgery		
	<i>N</i>	%	<i>N</i>	%	<i>N</i>	%	<i>p</i>
Gender							
Women	13	27	5	21	8	32	0.52
Men	36	73	19	79	17	68	
Comorbidity							
Coronary artery disease	12	25	4	17	8	33	0.32
Heart failure	10	20	4	17	6	24	0.73
Arrythmia	9	18	4	17	5	20	1.00
Valvular disease	3	6	2	8	1	6	0.61
Hypertension	30	61	14	58	16	64	0.77
Cerebrovascular insult	6	12	3	13	3	12	1.00
COPD	10	20	6	25	4	16	0.50
Kidney failure	3	6	2	8	1	4	0.61
Diabetes mellitus	10	20	7	29	3	12	0.17
Anthropometrics	Median (IQR)		Median (IQR)		Median (IQR)		<i>p</i>
Height, cm	49	172 (166–178)	24	172 (164–179)	25	174 (166–178)	0.84
Weight, kg	49	73 (65–84)	24	70 (62–81)	25	75 (68–87)	0.16
Body mass index, kg/m <sup>2</sup>	49	24.6 (23.4–28.4)	24	24.1 (22.1–28.1)	25	25.2 (23.8–30.5)	0.24

Abbreviations: COPD, Chronic obstructive pulmonary disease; *p*, Fischer's exact test; IQR, interquartile range.

## APPENDIX 2

### RESULTS FROM PREOPERATIVE CARDIOPULMONARY EXERCISE TEST FOR PATIENTS WHO WERE AND WERE NOT SELECTED FOR OPERATION.

	Total			Not selected for surgery			Selected for surgery			<i>p</i>
	<i>N</i>	Median	IQR	<i>N</i>	Median	IQR	<i>N</i>	Median	IQR	
Peak power, watt	49	85.0	68.0–115	24	74.0	61.8–90.0	25	100.0	81.0–132.0	0.007
% predicted peak power, (%)	49	59	46–82	24	50	38–62	25	68	55–92	0.002
Peak VO <sub>2</sub> , ml/min	49	1240	996–1697	24	1100	931–1321	25	1356	1140–1833	0.006
Peak VO <sub>2</sub> , ml/kg/min	49	17.1	14.1–20.6	24	15.5	12.9–19.7	25	18.5	15.3–22.4	0.006
% predicted peak VO <sub>2</sub> , (%)	49	77	58–96	24	60	51–88	25	91	70–104	0.002
VO <sub>2</sub> at AT, ml/kg/min	45	12.6	11.0–15.1	21	12.5	10.0–14.5	24	12.8	11.2–15.6	0.35
VE/VCO <sub>2</sub> slope	46	34.4	29.7–41.2	21	40.1	32.9–43.0	25	30.8	29.0–37.4	0.02
EqCO <sub>2</sub> nadir	47	32.7	28.8–37.6	22	34.8	30.2–39.3	25	30.8	27.9–34.1	0.58

Abbreviations: EqCO<sub>2</sub>, ventilatory equivalent for carbon dioxide; IQR, interquartile range; *p*, Independent-Samples Mann–Whitney *U* Test for comparison between patients who sustained versus did not sustain a postoperative complication; VO<sub>2</sub>peak, peak oxygen uptake; VCO<sub>2</sub>, carbon dioxide elimination; VE, minute ventilation.